APOLIPOPROTEIN E4 AND A CHANGE IN EPISODIC MEMORY FUNCTIONING AMONG NORMAL AGING NORWEGIAN ADULTS

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DEDICATION

This work is dedicated to my entire Family. To my parents Mr. and Mrs. Ananga and my entire siblings, whose love, care, determination and support had always inspired me to come this far. As a sign of appreciation and gratitude, it is a moment of great joy to express my sincerest thanks to all of you for such a wonderful and enduring attention.

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Thank You All

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ABSTRACT

The e4 allele of the apolipoprotein E (APOE) gene is a known risk factor for Alzheimer's disease and may also affect cognitive performance in normal aging. The data presented in the current study represent the first two time points of an ongoing longitudinal study examining cognitive changes in genetically at-risk individuals with much emphasis on test of episodic recall as measured by the California Verbal Learning Test. A total of 110 of 139 people who participated in the first phase of the study were used in the final analysis. Results indicate that there was no significant decline in cognition within participants over time. However, there was significant mean differences based on apoe4 status (participants with positive apoe4 allele have lower average mean scores than participants with negative apoe4 allele (both on short and long delay recall). In addition, there were significant interactive effects between apoe4 genotype and age (only on short delay recall) with the difference between the positive and negative larger for the older adults group. Gender also failed to produce any significant differences. It is concluded that, more complete understanding of the relationship between genes and memory requires consideration of a variety of factors. Several genes in interaction might account for a considerable portion of memory performance. After several candidate genes are known, this may be a fruitful approach.

Key Words: Apolipoprotein (APOE), Episodic memory, California Verbal Learning Test (CVLT), Cognition.

CHAPTER ONE

INTRODUCTION

One of the absolute certainties of life is aging. In many populations the proportion of elderly people is growing steadily, particularly the proportion of the more elderly. Aging is accompanied by a progressive but variable deterioration in health. The importance of aging is obvious in both the decline of cognitive function in the elderly and the vulnerability of the aging nervous system to degenerative diseases (Drachman 1997).

Investigators involved in aging studies have recognized the importance of separating pathologic changes from those that could be attributed to aging per se. Thus, for physiologic studies careful guidelines have been developed to exclude individuals whose age-determined responses and behaviors might be contaminated by specific disease processes (Rowe and Khan 1987). Results from the population remaining after such exclusions have then been interpreted as representing “normal" aging.

Within the category of normal aging, a distinction can be made between usual aging, in which extrinsic factors, such as diet, exercise, personal habits, and psychosocial factors, heighten the effect of aging alone, and successful aging, in which extrinsic factors play a neutral or positive role (Rowe and Khan, 1987). Genetic factors, life style, and community investments in a safe and healthy environment are important aspects of successful aging. The people in the usual aging group would perform at a lower level than they did previously, and those in the successful aging group would be able to continue active and creative lives. Nonetheless, the problem of normal / abnormal definition will recur (Rowe and Khan, 1987). Although age-based generalizations of declining cognitive functioning relating to younger subjects have dominated the literature, the heterogeneity of cognitive aging is beginning to attract serious attention. Increased variability in performance is reported among older subjects on a range of tests with significant numbers of older subjects performing within the range of younger subjects as found by Daffner and colleagues in 1994.

Cognition refers to "all aspects of perceiving, thinking and remembering" (Dorland’s Illustrated Medical Dictionary, 1988 cited in Johnson et al, 2005). The main domains of

cognition are memory, executive functions, abstraction, problem solving, visuospatial ability, and language (Johnson et al, 2005).

Many different types of models and terms are used by different authors to describe memory functions. Squire and Zola-Morgan (1988) proposed a distinction between declarative and non-declarative memory. Declarative (explicit) memory refers to conscious recollections of facts and events and depends on the integrity of the medial temporal lobe. In particular, the hippocampus, has an integrative and temporary role for encoding new memories and binding together the different memory stores of the neocortex. During information processing, structural or plastic changes occur in the synapses associated with learning, and more permanent memory develops (DeKosky and Scheff 1990). Throughout adult life, all physiological functions gradually decline. There is a diminished capacity for cellular protein synthesis, a decline in immune function, an increase in fat mass, a loss of muscle mass and strength, and a decrease in bone mineral density (Rudman and Rao 1992). Part of the aging process affecting body composition might be related to changes in the endocrine system (Rudman and Rao 1992, Lamberts et al 1997).

Non-declarative (implicit) memory comprises a heterogeneous collection of learning and memory abilities, all of which are nonconscious and expressed through performance. The formation of non-declarative memory is independent of the medial temporal lobe (Squire and Zola-Morgan 1991). Basal forebrain and lateral temporal cortex are regions likely to be involved in storing representations of acquired information (Squire and Zola-Morgan 1991).

Tulving (1989) suggested that there are three systems: procedural, semantic and episodic memory. Procedural memory refers to learned connections between stimuli and responses, which are not accessible to consciousness. Semantic memory refers to a general knowledge of the world which is not linked to particular temporal-spatial context; it permits the organism to construct mental models of the world. Episodic memory refers to conscious recollection of personally experienced events and their temporal relations. Procedural memory supports semantic memory and semantic memory supports episodic memory.

Abilities such as abstract thinking, reasoning, understanding of logical relationships and many other cognitive functions are generally considered to be aspects of intelligence. A common cultural stereotype is that intelligence declines somewhat with normal aging. Early investigators concluded the same result in their studies (Miles and Miles 1932, Wechsler 1939 cited in Dennis and Cabeza 2008). However, it has become increasingly clear that

"general intelligence" cannot be said to deteriorate with age (Bayles and Kazniak 1987cited in Dennis and Cabeza 2008). A slowing of response and processing speed has been shown to make a major contribution towards the changes in intelligence test performances seen with aging.

The most common intelligence test, the Wechsler Adult Intelligence Scale (WAIS) is composed of multiple subtests. Scores on these subtests are combined to provide a sum total, usually expressed as an intelligence quotient (IQ). The marked relationship between education and IQ is illustrated in the results of Green (1969 cited Dennis and Cabeza, 2008). When Green separated the WAIS full scale IQ into component verbal IQ and performance IQ scores, verbal IQ showed an increase with older age, among the educationally matched age groups, whereas performance IQ showed a slight decline. In the 21-year Seattle Longitudinal Study (Schaie 1983) for those measures concerned with the recall and use of previously acquired knowledge, little evidence of deterioration was apparent until after 70 years of age. For those tasks involving more active and novel problem-solving, a greater age-associated decline was observed.

Horn and Donaldson (1976) suggested that adult age relationships can be understood if two types of intelligence are distinguished. The first, fluid intelligence is reflected in tests of memory span, figural relations, inductive reasoning, and most processes involved in acquiring new information. Fluid intelligence decreases with old age. The second type, crystallized intelligence, is the cumulative product of information previously acquired by the activity of fluid intelligence, and thus represents the store of culturally transmitted information. Crystallized intelligence is measured by tests like vocabulary definition, general information knowledge, comprehension, arithmetic ability, and reasoning with familiar material. Crystallized intelligence remains stable throughout most of the adult life.

As people age, they often complain of memory loss. Kral (1962 cited Hallikainen, 1998) introduced the term "benign senescent forgetfulness" to describe mild memory losses associated with aging that do not progress to a dementing illness. He distinguished it from the "malignant forgetfulness" of the organic amnesic syndrome and dementia. Although the concept of benign senescent forgetfulness has received considerable attention in the clinical aging literature, it has been criticized for being poorly operationalized and insufficiently validated (Crook et al 1986). The National Institute of Mental Health (NIMH) Work Group on Aging and Memory recommended abandoning the earlier term and proposed a set of criteria for diagnosing Age-Associated Memory Impairment (AAMI) to describe the

subjectively and objectively evidenced memory loss that may occur in healthy, elderly individuals in the later decades of their life (Crook et al 1986).

AAMI is characterized by complaints of memory impairment in tasks of daily life, substantiated by evidence of such impairment on psychological performance tests with adequate normative data. The tests employed should assess recent memory for verbal and nonverbal material. The AAMI is applied to people over 50 years of age, although this does not imply that such impairment is qualitatively different than in younger adults, although being less frequently seen. The term is also a nonspecific relative to aetiology and does not necessarily imply that disorder is nonprogressive (Crook et al 1986).

A comparable term, Age-Associated Cognitive Decline (AACD), was introduced by a working group of the International Psychogeriatric Association (Levy 1994) to describe a similar population. The AACD criteria allow a decline in any principal domain of cognition, not only in memory. In addition to AACD, ARCD (Age-Related Cognitive Decline) is included in the DSM-IV. The diagnostic criteria of ARCD are not detailed nor used in studies. ARCD is an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age.

Proposed research diagnostic criteria of AAMI (Crook et al 1986) includes men and women at least age 50 year, complaints of memory loss reflected in such everyday problems as difficulty remembering names of individuals following introduction, misplacing objects, difficulty remembering multiple items to be purchased or multiple tasks to be performed, difficulty remembering telephone numbers or zip codes, and difficulty recalling information quickly or following distraction. Onset of memory loss must be described as gradual, without sudden worsening in recent months. It further includes memory test performance that is at least 1 standard deviation below the mean established for young adults on a standardized test of secondary memory (recent memory) with adequate normative data.

Apolipoprotein e4 and cognitive decline

The Apopoliprotein represent a diverse set of proteins that have in common their presence on plasma lipoproteins that transport cholesterol, triglycerides, and phospholips from one tissue or cell type to another. Thus, the apolipoproteins play a major role in lipid homeostasis, more importantly on the determination of the levels of cholesterol. Several types of apolipoproteins, including A B C D E H, and J and a number of subclasses, have been reported. Of these apolipoprotein E (APOE) has been the subject of particular scrutiny. Initial interest centered on its role as a regulator of plasma lipids levels. However, studies by Corder

et al, 1993 and Strittmatter et al, 1993 identified APOE as a major risk factor for the neurodegenerative disorder Alzheimer's Diseases which later sparked extensive research on the role of APOE in neurobiology. Since then, APOE has emerged as an important factor for several processes not obviously related to lipid metabolism, including neurite outgrowth and differentiation, neuronal repairs, and immno-regulations (Mahley & Rall, 2000).

The APOE protein is a 299 amino acid and it is synthesized in most organs, with the largest concentration found in the liver (about two thirds of the total plasma APOE) and the second largest concentration (one-thirds of the level seen in the liver) is found in the brain (Elshourbaby et al., 1985 cited in Mahley and Rall 2000). In the central nervous system, that APOE is synthesized and secreted primarily by astrocytes (Boyles et al., 1985), although recent studies suggest that APOE may be produced by neurons under diverse physiological and pathological conditions (Xu et al., 2006). The encoding gene is located at chromosome 19 and it is a polymorphic gene with 3 common alleles (E2, E3, E4) (Zannis et al, 1981 cited in Mahley and Rall 2000). The protein isoform differ at only 2 amino acid residues; 112 and 158. Although the structure difference between the APOE isoforms may seem small, it has significant impact on ultimate function. The single amino acid change appears to alter the overall conformation of the protein and thereby modifying its preference for specific types of lipoproteins, affecting its intraceluller handling by cells, and modulating its biological activity with respect to in-vitro effects on neurons and in-vivo effects on CNS structure and functions (Mahley & Huang, 1999 cited in Mahley and Rall, 2000). In general, E3 seems to be the normal isoform in every known function of the protein, whereas E4 and E2 can each be dysfunctional (or in some cases protective) for instance E2 has been associated with inheritance of type III hyperlipoproteinemia (Uttermann, 1987 cited in Mahley and Rall, 2000), but also with decreased incidence of both Alzheimer diseases and cardiovascular diseases (Corder et al., 1993). APOE4 has been associated with increased risk for and /or severity of a number of chronic conditions, with Alzheimer Diseases being the most acknowledge (Corder et al., 1993; Strittmatter et al., 1993). Furthermore, studies of healthy subjects found that E4 is associated with diminished CNS glucose utilization, for instance, Reiman et al, (2004) and increased decline in cognitive functions (e.g. Deary et al., 2002). Taken together, APOE appears to have global effect in the CNS.

Conceptual/ Theoretical Framework

Although several theories of memory exist today, most investigators would agree that memory can be subdivided into two broad categories: working memory (or short-term) and long-term memory. Long-term memory can in turn be divided into subsystems, one being episodic memory. Episodic memory refers to the conscious recollection of unique personal experiences in terms of their content (what), location (where), and temporal occurrence (Tulving, 2001). Episodic memory is typically assessed by first presenting some information (e.g., episodes, words, objects, or faces), and by then asking the person to recall or recognize the earlier-presented information. Episodic memory, which enables humans to consciously recollect personally experienced past events, is based on at least two fundamental mnemonic operations: memory formation and retrieval.

Encoding studies typically fall into one of three groups: intentional encoding studies, incidental encoding studies (both using blocked designs), and subsequent memory studies. During intentional encoding studies, participants are scanned while attempting to memorize words, faces, objects, or spatial routes, whereas, during incidental encoding, participants are usually asked to make a judgment (i.e., semantic, size) concerning stimuli during encoding, with no overt attempts at memorizing. Finally, in subsequent memory studies, activity associated with successful encoding operations is identified by comparing activity for items that are subsequently remembered to items that are subsequently forgotten (Paller & Wagner, 2002).

As with encoding, the literature regarding aging and imaging in retrieval can also be broken down into three main categories of study: recognition, recall, and context memory. In recognition studies participants are shown items presented at encoding along with new items and asked to judge whether they recognize the item as old or new, whereas recall studies require participants to freely generate that which was presented during encoding. Finally, context memory involves remembering not just the individual item presented at encoding, but also in what context (i.e., temporal order, colour, location) it was presented. Again, the most consistent findings from all three types of retrieval studies are discussed below

Event related functional MRI (fMRI) provides a unique opportunity to study the neural correlates of these processes and their subcomponents, such as successful and failed encoding (Dale & Buckner, 1997) Studies in young healthy subjects have shown that successful declarative memory formation, measured as the difference in brain activity during encoding

between subsequently remembered and forgotten items, is accompanied by increases in activity in medial temporal and inferior prefrontal areas. (Weis et al, 2004)
Structures within the medial temporal lobe (MTL) region, especially hippocampal formation, (Otten, Hensen & Rugg, 2001) are believed to be essential in establishing new memories.
Patients with mild cognitive impairment (MCI) are characterised by significant memory impairment, which is not severe enough to interfere with usual activities of daily living. The majority of patients with MCI go on to develop Alzheimer's disease (AD). Patients with AD, in comparison with older controls, show consistently decreased MTL activation during encoding of new materials (Spellinget al, 2003). Fewer fMRI studies have investigated MTL encoding activation in patients with MCI, (e.g. Dickerson et al, 2004) showing inconsistent results. A recent fMRI study showed decreased MTL activation during a memory encoding task (Machulda et al, 2003). However, a previous study by Small and colleagues (1999) found that only a subgroup of subjects with ''isolated memory decline'' demonstrated decreased hippocampal activation during encoding, whereas still another study (Bookheimer et al, 2000) reported increased MTL activation in cognitively intact individuals genetically at risk for AD. The variability in these fMRI results may be because the groups differed in the degree of impairment and underlying neural pathology.

Although the number of functional neuroimaging studies of cognitive aging has dramatically increased during the last decade, very few of these studies have made direct contact with cognitive aging theories. One reason, according to Dennis and Cabeza (2008), is that cognitive aging theories were originally developed to account for age-related differences in behaviour, and hence, they do not usually make predictions regarding the effects of aging on brain activity. A second reason is that these theories typically try to explain deficit in cognition and they rarely include hypotheses regarding compensatory mechanisms. In contrast, the notion of compensation is a central concept in the domain of functional neuroimaging of aging.

According to the sensory deficit theory, age-related deficits in sensory processing play a major role in age-related cognitive decline (Lindenberger & Baltes, 1994). Consistent with this view, older adults show considerable deficits in basic sensory functioning, including simple vision and auditory processing (Schneider & Pichora-Fuller, 2000). The main evidence for the sensory deficit theory comprises findings of strong correlations between age-related differences in sensory and cognitive measures (e.g., Baltes & Lindenberger, 1997).

Craik and collaborators (Craik, 1986; Craik & Byrd, 1982 cited in Dennis and Cabeza, 2008)) suggested that aging is associated with a reduction in the amount of attentional resources, which results in deficits in demanding cognitive tasks. A corollary of the resource deficit theory, the environmental support hypothesis (Craik, 1986 cited in Dennis and Cabeza, 2008), predicts that age-related differences should be smaller when the task provides a supportive environment which reduces attentional demands. Among other findings, the resources deficit theory is supported by evidence that when attentional resources are reduced in younger adults, they tend to show cognitive deficits that resemble those of older adults (Anderson et al., 1998).

One of the most popular cognitive aging theories is that older adults' cognitive deficits reflect a general reduction in the speed of cognitive processes (Salthouse, 1996). According to Salthouse (1996), low processing speed is assumed to impair cognitive performance because of two mechanisms: the time required by early operations reduces the time available for later operations (limited time mechanism), and the products of early operations are lost or irrelevant by the time later operations are completed (simultaneity mechanism). This view is supported by evidence that processing speed declines steadily with age, that this slowing shares considerable variance with age-related deficits in cognitive measures, and that processing speed is a strong mediator of cognitive decline in structural equation models.

CHAPTER TWO
LITERATURE REVIEW

A number of previous studies have looked for associations of the *APOE* genotype with cognitive functioning in samples without dementia. Anstey and Christensen (2000) have reviewed the evidence from longitudinal studies of cognitive change in older individuals. They found fairly consistent evidence that the e*4* allele predicts decline in memory and processing speed but not in crystallized or fluid abilities. However, the results are complicated by the fact that some people who were included in these studies later developed dementia, whereas other studies excluded them.

There are fewer studies looking at the effect of the *APOE* genotype on cognitive functioning in young and middle-aged adults. The e*4* allele does not appear to be related to lower scores on intelligence tests in either children (Deary et al., 2002) or adults who are in their 20s (Yu, Lin, Chen, Hong, & Tsai, 2000). Given that episodic memory is affected early in AD, it might be expected that *APOE* genotype would affect memory tasks earlier in life. However, the evidence from middle-aged samples is largely negative. Flory, Manuck, Ferrell, Ryan, and Muldoon (2000) found that, in a healthy community sample of adults with a mean age of 46 years, the e*4* allele was associated with poorer episodic memory performance.

Transgenic mice expressing human APOE ε4 develop an age-dependent decline in memory without pathological features of Alzheimer's disease (AD). This implicates APOE in the maintenance of memory during normal senescence, but parallel human studies are limited because longitudinal investigations of memory usually do not exclude patients with AD or "questionable" AD (QD). Mayeux et al (2000) examined the effect of APOE on cognitive function over time in elderly without dementia. They hypothesized that compared to other APOE alleles memory decline even in healthy elderly would be greater among those with an APOE ε4. The results of neuropsychological tests, grouped into domains of memory, language and visuospatial/cognitive function by factor analysis, were examined at three intervals over a seven-year period in 563 healthy elderly without AD or QD using generalized estimating equations. Memory performance declined over time, while scores on the visuospatial/cognitive and language factors did not change. Increased age was associated with lower scores and higher education with higher scores on all factors at each interval. No APOE allele was associated with performance on a specific cognitive factor at any interval,

but the presence of an APOE ε4 allele was associated with a more rapid decline in the memory factor over the follow-up period. The effect was most pronounced among individuals with less than 10 years of formal education. There was no similar time-dependent relationship between APOE ε4 and the language or visuospatial/cognitive factors. Transgenic mice and elderly humans without AD or QD expressing APOE e4 show a decline in memory performance over time. They concluded that these observations provide evidence for an APOE-specific effect on memory during senescence.

In a study by Caselli et al, (1999) to determine, in a cross-sectional evaluation of non-demented individuals, if age-related memory decline is influenced by apolipoprotein E genotype, tests of immediate and delayed recall (primary outcome measures) and other neuropsychological measures (secondary outcome measures) were given to three genetically defined groups of cognitively normal individuals (age, 49 to 69 years) including apoE-4 homozygotes (n = 25), APOE ε4 heterozygotes (n = 25, all epsilon3/4), and apoE-4 non carriers (n = 50). Groups were matched for age, gender, and educational background. Cross-sectional comparisons between the genetic subgroups of the relationship between age and test score were performed for each neuropsychological measure. Results indicates that there were no intergroup differences in mean scores on any neuropsychological measure, but tests sensitive to immediate and delayed recall showed a significant negative correlation with age in the APOE ε4 homozygote group relative to the non carrier group. Consistent with previous neuropsychological studies of early AD, this cross-sectional study suggests that age-related memory decline occurs earlier in cognitively healthy APOE ε4 homozygotes than in APOE ε4 heterozygotes and non carriers, and precedes clinically detectable AD.

Non-demented older adults genotyped for the Apolipoprotein E e4 allele *(n* = 43) were neuropsychologically compared to participants without a copy of the e4 allele *(n* = 90) by Bondi et al (1999). At baseline, the groups did not differ on age, education, gender, or global cognitive status. ApoE-e4 participants demonstrated significantly poorer mean performances on delayed recall, but no significant group differences emerged on attention, language, constructional skills, psychomotor speed, or executive function. Significantly more ApoE-e4 participants developed probable or questionable Alzheimer's disease (AD) compared with non-e4 participants, suggesting that the group differences resulted from a preponderance of preclinical AD cases within the e4 group and not from a direct influence of ApoE genotype on cognition. Cox proportional hazards analysis, adjusting for age, years of education, and

global cognitive status, revealed that APOE ε4 allele status and measures of recall performance were significant and independent predictors of conversion to AD. Results support the importance of specific episodic memory changes and possession of the ApoE e4 allele in the preclinical detection of AD.

To investigate whether the association between APOE-epsilon 4 and memory decline modified by baseline cognition and age in a population-based elderly sample, Dik et al (2000) studied sample consisting of 1,243 subjects, 62 to 85 years old, with a Mini-Mental State Examination (MMSE) score between 21 and 30 and known APOE phenotypes. Memory performance was measured with an abbreviated Auditory Verbal Learning Test (AVLT) at baseline and repeated after 3 years (n = 854). Memory decline was defined as a decrease of at least 1 SD from the mean change score on immediate recall (IR), delayed recall (DR), and retention, based on the AVLT. Results indicated that multivariate logistic regression analyses showed APOE-epsilon4 is associated with memory decline in cognitively impaired subjects (MMSE score, 21 to 26) (OR for decline on IR adjusted for age, sex, education, and baseline recall score, 3.8; 95% CI, 1.4 to 10.0; adjusted OR for decline on DR, 2.9; 95% CI, 1.2 to 7.0; adjusted OR for decline on retention, 3.3; 95% CI, 1.1 to 10. 1), but not in cognitively normal subjects (MMSE score, 27 to 30) (adjusted OR for decline on IR, 1.1; 95% CI, 0.6 to 2.0; adjusted OR for decline on DR, 1.0; 95% CI, 0.6 to 1.8; adjusted OR for decline on retention, 1.5; 95% CI, 0.7 to 3.0). In particular, cognitively impaired epsilon4 carriers older than 75 years were at high risk of memory decline (adjusted OR for decline on IR, 4.5; 95% CI, 1.4 to 13.8; adjusted OR for decline on DR, 3.6; 95% CI, 1.2 to 10.8; adjusted OR for decline on retention, 6.6; 95% CI, 1.5 to 29.7). APOE-epsilon4 was associated with memory decline in subjects with cognitive impairment, but not in normally functioning subjects, contrary to AD studies, and concluded that their study suggests the risk of APOE-epsilon4 on memory decline does not decrease at higher ages.

Impairment of episodic memory is an early and defining feature of Alzheimer disease (AD). The apolipoprotein E (APOE) e4 allele is known to influence risk of AD but it has been difficult to establish whether it affects episodic memory differently from other cognitive functions. To examine the association of e4 with decline in different cognitive systems Wilson et al, (2002) used a longitudinal cohort study with more than 40 groups of Catholic clergy from across the United States. Participants were Older Catholic clergy members without clinical evidence of dementia at baseline underwent annual clinical evaluations for up

to 6 years. Of 624 persons eligible for follow-up, 611 (98%) participated, of whom 161 (26%) had at least 1 e4 allele. They completed an average of 5.5 evaluations (range, 2-7). Main outcome measures were that of incident AD and annual rates of change in episodic memory, semantic memory, working memory, perceptual speed, and visuo-spatial ability. Results indicate that the presence of e4 was associated with risk of developing AD on follow-up (relative risk, 1.92; 95% confidence interval, 1.27-2.89). In a series of random effects models, e4 was associated with impaired baseline function in episodic memory and visuospatial ability and with more rapid decline in all domains. The effect of e4 on annual decline in episodic memory (>3-fold increase) was significantly stronger than its effect on decline in other cognitive systems (P<.01), and at baseline, its effect on episodic memory was marginally stronger than its effect on other cognitive domains (P=.06). Wilson et al (2002) concluded that the results suggest that the APOE ε4 allele influences risk of AD by a relatively selective effect on episodic memory.

Baxter and colleagues (2003) examined memory decline as a function of APOE status and age in cognitively intact participants aged 48–77 years old. Participants were grouped by age (<60 versus ≥60) and APOE (ε4+/−). Longitudinal analysis of several components of memory over a 2-year interval showed a significant Age-by-APOE interaction reflecting a decline in new learning for the ≥60 ε4+ group only. Among ε4+, 76% of the ≥60 participants showed a decline versus 32% of the <60, but the amount of decline in new learning over the 2-year interval within the ≥60 group was not further influenced by age. That is, the size of the 2-year change was the same for 60 and 70 year old participants. This suggests that longitudinal study of new learning is a sensitive measure for detecting early cognitive changes in at-risk individuals that precede the symptomatic onset of mild cognitive impairment and AD.

To assess the role of the ε4 allele of the *APOE* gene in longitudinal cognitive decline Bretsky et al (2003) longitudinally assessed multiple measures of cognitive function in the MacArthur Successful Aging Study, a population-based cohort free of frank impairment at baseline. Subjects were 965 Caucasian and African American men and women aged 70 to 79 years, who completed two follow-up evaluations, one at 3 years and another at 7 years. At the first follow-up, modest but significant declines in naming and spatial ability were associated with the APOE ε4 genotype. By the second follow-up, more pronounced and significant associations were noted between the APOE ε4 genotype and cognitive decline from six of the

eight cognitive outcomes. After 7 years, APOE ε4 allele carriers were twice as likely to have declined on a global cognitive score (odds ratio = 2.0; 95% CI: 1.1, 3.6) as non carriers. Bretsky and colleagues concluded that APOE ε4 is associated with cognitive decline among a high-functioning elderly cohort, with effects most pronounced after 7 years of follow-up. Hence, the ε4 allele either may function as a risk factor for cognitive impairment in normal aging across a broad spectrum of domains or may exert detectable effects early in a long prodromal AD trajectory.

Greenwood et al (2005) examined the cognitive consequences of the apolipoprotein E–e4 allele in middle age, before likely onset of symptoms of Alzheimer's disease. The authors identified 3 cognitive processes—visuospatial attention, spatial working memory, and the effect of visuospatial attention on working memory—and devised "behavioral assays" of the integrity of components of these processes. Redirecting visuospatial attention, retention of memory for location, and attentional modulation of memory of target location were affected by APOE genotype. Visuospatial attention showed additive effects of e4 gene dose; each additional e4 allele inherited further slowed disengagement from invalidly cued space. In contrast, working memory performance was affected only in e4 homozygotes. Effect sizes for the APOE gene were moderate to large, ranging from 14% to 24%. They concluded that effects of APOE genotype on component processes of cognition in healthy, middle-aged adults are consistent with the emergence in adulthood of an APOE ε4 cognitive phenotype.

In a prospective cohort study, the Nilson et al (2006) demonstrated a more pronounced epsilon4-related deficit for participants 70 years of age and older in tasks assessing episodic recall. Apolipoprotein E and age interacted for episodic memory tasks, whereas the interaction for semantic memory tasks was between APOE and test wave. Heterozygotes of epsilon4 between middle-age and young-old participants performed at a higher level than non carriers of this allele in recall tasks. A dose effect was found such that carriers of 2 epsilon4 alleles failed more profoundly in acquiring and recollecting episodic information than carriers of 1 epsilon4 allele, who in turn failed more than carriers of non-epsilon4 alleles. The pattern of findings observed for older epsilon4 carriers suggests that these individuals have particular difficulty when the executive task demands are high. Several factors (e.g., smaller hippocampal volumes, less effective neural repair mechanisms) may account for these findings. On the basis of the data obtained, the authors argue that analyses of the effect of

specific genes in cognition should be accompanied by assessment of performance at a specific level, with due attention to the individual's age.

Memory declines more rapidly with age in apolipoprotein E e4 carriers than in *APOE* e4 non-carriers, and *APOE* e4 homozygote's' cognitive performances correlate with stressors. These changes could represent pre-symptomatic disease in some, despite their youth. A study was undertaken to show that pre-symptomatic *APOE* e4 homozygotes experience greater psychometric decline at a younger age than *APOE* ε4 heterozygotes and non-carriers before the diagnosis of mild cognitive impairment (MCI) and Alzheimer disease (AD). In a prospective observational study at an academic medical center, a total of 43 *APOE* e4 homozygotes, 59 *APOE* e4 heterozygotes, and 112 *APOE* 4 non-carriers aged 50 to 69 years were cognitively healthy and matched at entry according to age, educational level, and sex by Caselli et al (2007). Of 214 participants, 48 showed no decline on any test, 126 showed declines on only 1 test in 1 or more domains, and 40 showed decline on 2 or more tests in 1 or more domains. Cognitive domain decline occurred in 4 of 10 *APOE* e4 homozygotes 60 years and older at entry (40.0%) compared with 5 of 66 *APOE* ε4 heterozygotes and non-carriers (7.6%) (*P*=.02) and was more predictive of subsequent decline than non domain decline (17 of 24 [70.8%] versus 29 of 70 [41.4%]; *P*=.01). Decline on any memory test was predictive of further decline (*P*<.001), as was memory domain decline (*P*=.006) in all genetic subgroups. Seven participants developed MCI (in 6) or AD (in 1), of whom 5 were *APOE* ε4 homozygotes (*P*=.008). Retrospective comparison showed that those who experienced multi domain, memory, and language domain decline had lowered spatial and memory scores at entry than those who experienced no decline. APOE ε4 homozygotes in their 60s have higher rates of cognitive domain decline than APOE ε4 heterozygotes or non-carriers before the diagnosis of MCI and AD, thus confirming and characterizing the existence of a pre-MCI state in this genetic subset.

It must however be noted however some studies have come out with contradicting findings. Plassman et al (1997) examined the relation of APOE-epsilon 4, hippocampal volume, and cognitive performance in ten pairs of cognitively normal twins who had a mean age of 62.5 years (SD = 7.8). There were no significant differences in neuropsychological measures of the groups categorized by the presence of an epsilon 4 allele. However, the mean normalized right and left hippocampal volumes were smaller in the epsilon 4 groups compared to the

group without epsilon 4. Combined with prior reports, these findings suggest that epsilon 4 is associated with differences in brain morphology that may be evident when no symptoms of dementia are present.

Small et al (2000) examined the relationship between APOE genotype and cognitive functioning in normal aging, and to determine whether this relationship was moderated by age or the presence of a number of disease conditions, including cardiovascular disease and diabetes. The sample was drawn from the Charlotte County Healthy Aging Study, a community-based, cross-sectional study of randomly selected older adults in Charlotte County, FL. A total of 413 older adults (mean age = 72.90 years) were examined in the current study. Participants completed tasks that indexed a variety of dimensions of cognitive functioning, including episodic memory, implicit memory, psychomotor speed, and attention. In addition, participants provided self-reported and objective indices of health status and were genotyped for APOE. Mean-level results indicated that groups with and without the APOE-epsilon4 allele performed similarly on all domains of cognitive functioning. Significant age group differences were observed in episodic memory, psychomotor speed, and attention but not implicit memory. Significant gender differences were present for episodic memory and the Stroop test. Analyses also indicated that participants' age did not exert an impact on the relationship between APOE-epsilon4 and cognitive functioning. Further, the presence of cardiovascular disease or diabetes did little to moderate the relationship between APOE-epsilon4 and cognition. The authors found no evidence for a relationship between presence of the APOE-epsilon4 allele and cognitive functioning. Further, age or the presence of a number of chronic conditions did not significantly moderate the effect of APOE genotype on cognitive performance. These results indicate that the presence of the epsilon4 allele is not a risk factor for cognitive impairment in normal aging.

Because of the evidence suggesting that the association between the apoE-e4 allele and AD decreases in the very oldest old and that the role of APOE ε4 in relation to memory might differ depending on subjects' age, Salo et al (2001) wanted to study whether an association might exist between the APOE genotype and either learning or memory in the non demented oldest old. Two questions were studied: First, are learning and memory poorer in the oldest old (aged 85 years and older) non demented e4 carriers than in e4 non carriers? And second, are learning and memory better in those with the e2 allele than in those with other alleles? The objective of their study was to analyze the relationship of the apolipoprotein E e4 and e2

alleles to learning and memory performances in the non demented oldest old. Forty-six non demented persons aged 85 years or over from a randomly selected group of 128 subjects in Vantaa, Finland, were studied. APOE genotyping was performed using the mini sequencing technique. A structured clinical examination and interview were carried out. The test variables studied were learning and memory scores (from the Fuld Object-Memory Evaluation), verbal fluency, and conceptualization (the Similarities subtest of the WAIS-R). They compared APOE ε4 carriers to non carriers and APOE ε2 carriers to non carriers. No statistically significant differences were found in any of the test variables. The results failed to confirm the hypotheses that poor cognitive performance is associated with the apoE-e4 allele and good performance with the APOE ε2 allele in the oldest old. This suggests that the APOE alleles do not have a detectable relationship to learning and memory in non-demented very elderly people.

The neurobiological changes underlying the association of the apolipoprotein E (APOE) e4 allele with level of cognition are poorly understood. To test the hypothesis that amyloid load can account for (mediate) the association of the APOE ε4 allele with level of cognition assessed proximate to death, 44 subjects with clinically diagnosed Alzheimer's disease and 50 without dementia, who had participated in the Religious Orders Study, underwent determination of APOE allele status, had comprehensive cognitive testing in the last year of life, and brain autopsy at death by Bennet et al (2005). The percentage area of cortex occupied by amyloid beta and the density of tau positive neurofibrillary tangles were quantified from six brain regions and averaged to yield summary measures of amyloid load and neurofibrillary tangles. Multiple regression analyses were used to examine whether amyloid load could account for the effect of allele status on level of cognition, controlling for age, sex, and education. Possession of at least one APOE ε4 allele was associated with lower level of cognitive function proximate to death ($p = 0.04$). The effect of the e4 allele was reduced by nearly 60% and was no longer significant after controlling for the effect of amyloid load, whereas there was a robust inverse association between amyloid and cognition ($p = 0.001$). Because prior work had suggested that neurofibrillary tangles could account for the association of amyloid on cognition, Bennet et al (2005) next examined whether amyloid could account for the effect of allele status on tangles. In a series of regression analyses, e4 was associated with density of tangles ($p = 0.002$), but the effect of the e4 allele was reduced by more than 50% and was no longer significant after controlling for the effect of amyloid

load. These findings are consistent with a sequence of events whereby the e4 allele works through amyloid deposition and subsequent tangle formation to cause cognitive impairment.

Taking all the evidence together, one can conclude that people who develop AD show cognitive differences many decades before the onset of the disease. However, the cause of these differences is not established. There are possible roles for preclinical disease, protective effects of cognitive reserve, and lifestyle factors associated with cognitive ability that affects risk for AD.

Given that these early differences exist, which cognitive functions are most affected? Backman, Jones, Berger, Laukka, and Small (2005) carried out a meta-analysis of studies that assessed cognitive functioning in a sample without dementia and then followed the sample to see who developed AD and who did not. Looking at various kinds of cognitive tests, they found the largest effect sizes (>1 standard deviation unit) for tests of global cognitive functioning, episodic memory, speed, and executive functioning. Tests of verbal ability, attention, and spatial ability were also found to discriminate. The only domain that did not discriminate was short-term memory, which included digit span. The pattern of results was similar for studies with longer as opposed to shorter follow-ups. If there are very early preclinical effects of AD, then it would be expected that risk factors for AD would be related to cognitive functioning earlier in the life span. One of the most consistently replicated risk factors for AD is the apolipoprotein E (APOE) genotype. The e*4* allele is known to increase risk for AD and the e*2* allele to decrease risk. Furthermore, the e*4* allele increases risk for ischemic cerebrovascular disease (McCarron, Delong, & Alberts, 1999 cited in Båckman et al, 2005), which may also contribute to age-related cognitive deficits. The e*4* allele has also been reported to be more frequent in cases of mild cognitive impairment, which fall short of satisfying diagnostic criteria for dementia (Collie & Maruff, 2002). It might therefore be expected that the *APOE* genotype would be related to cognitive functioning in persons without dementia and that this association would become more apparent with age as the risk of preclinical AD increases.

Gender differences in memory

Being able to remember events from one's past is essential for functioning in society. By now, it is well known that a number of factors, among them age and education, affect one's ability to remember. Whether one's sex also influences the ability to remember every day

events is less well researched. One reason may be that, in the first comprehensive review of this subject, Maccoby and Jacklin (1974) did not find sex difference in memory. However, the theoretical model often used by those researchers was different from that of current theories, which may explain why they did not find sex differences.

What impact does task material have on sex difference in episodic memory? Although Maccoby and Jacklin (1974) did not find sex difference in memory, many more recent studies have found sex difference favouring women in episodic memory tasks. For example, in a large population-based study of 1,000 adults between 35 and 80, we found sex difference on episodic memory tasks in which the participants were told to try to remember lists of words, objects, or activities that had been presented earlier (Herlitz, Nilsson, & Bäckman, 1997). The difference between men and women on a word recall task was d 5 .25 d is computed by calculating the difference between the means of women and men, divided by the pooled standard deviation. Here, a positive value indicates that women perform at a higher level than men, and a negative value indicates that men out- perform women. The closer the value is to zero, the smaller the difference. A d of .20 indicates that 59% of all women perform at a higher level than the average man. The comparable numbers ford 5 .40 and d 5 .60 are 66% and 73%, respectively. Notably, most tests used to assess episodic memory in clinical situations, such as the California Verbal Learning Test and subtests of the Wechsler memory Scale, use similar materials as we did—that is, word lists, lists of objects, or pictures of objects. Women are typically found to perform at a higher level than men on these tests (e.g., Kramer, Delis, Kaplan, O'Donnell, & Prifitera, 1997). Maccoby and Jacklin (1974) noted that girls excel on verbal tasks and that boys perform at a higher level than girls on visuospatial tasks. Sex difference in verbal and visuospatial tasks have since then been confirmed in numerous studies (e.g. Voyer, Voyer, & Bryden, 1995). Because women excel on verbal-production tasks—for example, tasks requiring participants to rapidly retrieve words starting with the letter F (Hyde & Linn, 1988 cited in Voyer et al, 1995)—it may not be surprising that women also excel when they are asked to recall events that happened during the past year, day, or minute. Women may simply be at an advantage on such episodic memory tasks due to their superior verbal-production abilities. Analogously, as men typically perform at a higher level than women on visuospatial tasks—such as understanding what an irregular figure looks like when it is rotated in space (Voyer et al., 1995) men can be expected to perform at a higher level than women on episodic memory tasks requiring visuospatial processing. Although relatively few studies have examined sex difference in visuospatial

episodic memory tasks, it is clear that the pattern of sex difference is different than for verbal episodic memory tasks (Lewin, Wolgers, & Herlitz, 2001). The magnitude of the male advantage seems to vary as a function of the extent to which the task relies on visuospatial processing versus the extent to which verbal processing can be utilized. Of interest is also whether there is sex difference on episodic memory tasks requiring both verbal and visuospatial processing. Notably, women outperform men on tasks requiring remembering an object's position, such as when playing the game memory or when trying to remember where they last saw their keys (Voyer, Postma, Brake, & Imperato-McGinley, 2007). Thus, even though such tasks clearly require visuospatial processing, women may be able to use their verbal advantage to remember objects' positions. Are there sex difference on episodic memory tasks requiring minimal verbal or visuospatial processing, such as when remembering unfamiliar odours? This would be interesting to know, as the presence of sex difference on such tasks may suggest that there is an underlying sex difference in basic episodic memory capacity that is irrespective of the type of material to be remembered. Although not many studies have addressed this issue and more studies are needed, there are findings suggesting that women have a slight advantage over men on such tasks (Oberg, Larsson, & Bäckman, 2002).

The impact of verbal and visuospatial ability on sex differences in episodic memory was investigated. One hundred men and 100 women, 2040 years old, participated in a series of verbal and visuospatial tasks. Episodic memory was assessed in tasks that, to a greater or lesser extent, were verbal or visuospatial in nature. Results showed that women excelled in verbal production tasks and that men performed at a superior level on a mental rotation task. In addition, women tended to perform at a higher level than men on most episodic memory tasks. Taken together, the results demonstrated that (a) women perform at a higher level than men on most verbal episodic memory tasks and on some episodic memory tasks with a visuospatial component and (b) women's higher performance on episodic memory tasks cannot fully be explained by their superior performance on verbal production tasks.

Research shows sex differences in episodic memory. These differences vary in magnitude as a function of the type of material to be remembered. Throughout the life span, verbal episodic-memory tasks yield differences favouring women. In contrast, episodic-memory tasks requiring visuospatial processing result in differences favouring men. There are also sex differences favouring women on episodic-memory tasks requiring both verbal and

visuospatial processing and on face-recognition tasks. Thus, there may be a small, general episodic-memory advantage for women—an advantage that can increase by the advantage women have over men in verbal production and can be reversed by the male advantage in visuospatial tasks. In addition, environmental factors affect the magnitude of the sex differences in episodic memory. Among elderly people without dementia, the apolipoprotein E e4 allele (APOE4) has been associated with cognitive deficit, particularly in episodic memory, but few reports are available on whether this association differs by sex.

In a community-dwelling Norwegian cohort of 2181 elderly people (55% women), aged 70–74 years, episodic memory was examined in relation to sex and APOE4 zygosity by Lehman et al (2006), with the Kendrick Object Learning Test (KOLT). Possession of at least one APOE4 allele had a modest, detrimental effect on episodic memory in women, whereas in men, heterozygotes were unaffected and homozygotes had markedly lower scores across the distribution of KOLT scores. This sex difference was found consistently in all analyses: on comparing means and medians, examining trends across quintiles, and studying the distribution of scores and the risk of cognitive impairment. Results were broadly similar when adjusted for known determinants of cognition and also when severely impaired participants were excluded. The adjusted odds ratio (OR) of cognitive impairment in women was shown to be 1.8 (95% confidence interval (CI): 1.1 to 2.8) for heterozygotes and 1.1 (0.3 to 3.7) for homozygotes; the adjusted OR in men was observed to be 1.1 (0.6 to 2.1) for heterozygotes and 10.7 (4.7 to 24) for homozygotes. Lehman and colleagues (2006) concluded that although the harmful effect of APOE4 on episodic memory was modest in women, the risk was found to occur in about 30%. APOE e4 was observed to have a dramatic effect on episodic memory in men, but only in homozygotes, which comprised about 3% of men: the whole male homozygous group showed a marked shift to lower memory scores.

Subjects with mild cognitive impairment (MCI) have been shown to have reduced hippocampal volumes relative to normal elderly control subjects. The presence of the apolipoprotein E e4 allele has been associated with greater hippocampal atrophy in women than in men with Alzheimer disease. This relationship has not been demonstrated in MCI. To examine the relationship between APOE genotype and hippocampal volume in men and women with MCI, Fleisher et al, (2005) evaluated MCI in 193 subjects (86 women and 107 men) participating in a multicenter clinical trial, all of whom underwent magnetic resonance imaging at their baseline visit. They evaluated the association among the number of APOE e*4*

alleles, memory performance, and hippocampal volume in men and women with tests of means and multiple linear regressions. Compared with MCI subjects with no APOE *e4* alleles, women with 1 or 2 APOE *e4* alleles were found to have significantly reduced hippocampal volume, whereas men only showed a significant reduction in hippocampal volume when carrying 2 APOE e*4* alleles. Worsening of performance on a delayed word recall task (Alzheimer's disease Assessment Scale cognitive subscale) showed an identical pattern in association with APOE e*4* allele dose and sex. Furthermore, when controlling for memory performance on delayed word recall, the APOE e*4* effect on hippocampal volumes was attenuated in men, but remained significant in women. The APOE e*4* genotype status appears to have a greater deleterious effect on gross hippocampal pathology and memory performance in women than in men.

The relationship between apolipoprotein E (APOE) ε4 and change in cognition was examined in older men (n = 247; age = 75.0 ± 3.5 years) and women (n = 79; age = 70.8 ± 4.9 years) free of history of stroke by Swan and colleagues (2005). Participants were examined again 4.0 ± 0.5 years later. Exclusion criteria were (1) initial scores on the Mini-Mental State Examination of 23 or less or (2) the presence of the APOE 2/4 genotype. Men with ε4 showed greater decline in some measures of executive function and verbal memory compared to those without ε4; women with ε4 showed greater decline in Trail Making test performance relative to women without the allele. A significant gender × APOE ε4 interaction was seen for change in performance on short delay cued recall. These results suggest that APOE ε4 is associated with cognitive decline differently in older adult men and women.

The APOE epsilon 4 allele is overrepresented, and the apoE epsilon 2 allele underrepresented, in Alzheimer's disease. To assess the risk of cognitive impairment in individuals with these genotypes in the general population, Hyman et al, (1996) studied a population-based sample of 1,899 individuals 65 years and older as a follow-up to the Iowa 65+ Rural Health Study. Multiple regression and logistic regression analyses demonstrated significant effects of apoE epsilon 4 and APOE epsilon 2 in predicting performance on a delayed recall task over a 4- to 7-year period. The magnitude of this effect was, however, fairly modest, with odds ratios for developing impairment of approximately 1.37 (95% confidence interval: 1.007, 1.850; p = 0.045) for APOE epsilon 4 and 0.53 (95% confidence interval: 0.368, 0.777; p = 0.001) for apoE epsilon 2. These effects were more pronounced in women than men. Importantly, 85% of elderly apoE E4 individuals (average age, 81) scored

in the unimpaired range on a screening mental status test. Thus, many individuals reach old age without cognitive impairment despite inheritance of one or two apoE epsilon 4 alleles. This suggests that apoE genotyping will have limited utility as a diagnostic or prognostic indicator of cognitive decline in individuals.

To determine whether the APOE epsilon4 allele is associated with age-related intellectual decline in a community-dwelling sample of Danes, a sample of 189 subjects who did not have dementia was tested with the Wechsler Adult Intelligence Scale (WAIS) at the ages of 50 and 80 years by Mortensen and Høgh (2001). Of these subjects, 163 (84 women and 79 men) completed all WAIS subtests at both assessments and 139 completed the digit symbol and block design subtests at the ages of 50, 60, 70, and 80 years. Cognitive decline from the age of 50 to the age of 80 years was substantial and larger for the performance subtests than for the verbal subtests (the declines were 18.40 for the performance IQ and 8.39 for the verbal IQ). APOE genotype was unrelated to the observed WAIS results of the 80-year assessment, but there was a significant interaction between APOE genotype and sex for decline scores in the performance IQ and three performance subtests (digit symbol, block design, and object assembly). In women, 26 epsilon4 carriers showed larger decline than 58 non carriers, whereas there was no significant relation between APOE genotype and cognitive decline in men. The association in women between APOE genotype and cognitive decline was significant only for decline in the decade from age 70 to age 80 years. The interaction between sex and APOE genotype remained significant when education was included as a covariate. Mortensen and Høgh (2001) concluded that the APOE epsilon4 allele is associated with normal age-related decline in cognitive functions in women only. This finding may be supportive of recent evidence suggesting sex differences in APOE-associated risk for AD. Thus, the sex difference in the risk of sporadic AD may partly be explained by a sex-specific impact of the APOE e4 allele on age-related cognitive decline.

The above studies have demonstrated that non-demented individuals with a copy of the APOE allele performs worse on neuropsychological tests than non-carriers in particular on task that assess memory (e.g. Mayeux et al., 2000; Wilson et al., 2002 etc), however, other studies have found such effects (e.g. Plassman et al., 1997; Small et al., 2000 etc).

Several factors may account for the contradictory findings. First the influence of the APOE genotype may vary for different cognitive domains or sub-domains, meaning that the nature of the test may affect the likelihood of observing APOE4-related deficits. A meta-analysis (including 38 studies) by Small et al, (2004) showed that APOE4 carriers, as compared to non-carriers, had lower scores on test of global cognitive function, executive function and episodic memory, while no differences were observed for the domains of primary memory, attention, visuospatial skills, verbal ability or perceptual speed. In a recent longitudinal-based study by Nilson et al (2006), the APOE4-related deficits were primarily observed in test episodic memory, whereas little or no effect were seen in test of semantic memory, primary memory or priming. Further, episodic memory impairments were more pronounced in test of recall than in test of recognition memory. Nilson et al (2006) interpreted the findings of more salient deficits in recall than in recognition as reflecting problem with executive processes, such as attention and working memory. Indeed, these abilities have been found to be impaired among e4 carriers (Greenwood et al., 2005; Reinvang et al., 2005).

A possible explanation for the selective cognitive impairment concerns the neural seat for APOE4 related alterations. APOE4 has been associated with increased regional atrophy (Plassman et al, 1997) and hypo metabolism (Reiman et al, 2005), in frontal, parietal and temporal regions, including the hippocampal structure which is known to be crucial for episodic memory functioning (Cabeza & Nyberg, 2000). Parasuraman et al (2002), who found APOE4-attentional deficits, emphasized temporoparietal brain areas as possible locus of APOE4-related cognitive impairment by implicating the cholinergic neurotransmitter. However, overall biological mechanism through which the APOE genotype might affect cognition functions remained largely unknown. Although several neurobiological deficits have been associated with APOE4 allele as compared to the other e2 and e3 alleles, including less effective neuronal repair mechanism, a link between these effects and memory decline has not been conclusively demonstrated.

Other factors that might add to the inconsistent findings include small or unequal sample size, recruitment methods, and sample demographies. For instance, both Small et al (2004) and Nilson et al (2006) found that APOE e44 homozygotes performed significantly worse than e4 heterozygotes. Moreover, the pattern of cognitive deficit observed among APOE e4 allele loses some importance with age (Corder et al, 1993; Small et al., 2004), and test on children and young subjects have revealed no significant effects of the APOE genotype on Intelligent

Quotient (Yu et al, 2000), or on general cognitive ability (Deary et al, 2001). In fact, many longitudinal studies that report significant between- group differences in memory change over time see no or only small absolute difference at baseline in relation to APOE genotype, for instance, Nilson et al (2006).

Further, considering the strong association between APOE e4 and increased risk for AD, and that AD-related memory deficits commonly appear many years prior to clinical diagnosis (Ellias et al., 2000), a given question is whether the observed memory decline among APOE e4 carriers reflects yet undiagnosed dementia symptoms, or an influence of the APOE genotype itself.

AIMS AND OBJECTIVES OF THE STUDY

Alzheimer Disease is the most common form of dementia. It is characterized by a gradual loss of cognitive functions as a result of chronic neurogenerative disorder. More than 12 million persons are affected worldwide and with an aging population the number of AD cases steadily increasing. APOE4 has been identified as a major susceptibility gene for Ad by genetic studies. Results from brain imaging studies suggest that the non-demented APOE3-carriers have altercation in memory-related activities, and that these changes occur in brain regions that are pertinent to the disease. Given that the AD process likely begins years prior to the onset of the cognitive problem; it is tempting to interpret these findings as preclinical markers of improving dementia. However the existing studies are equivocal with regards to a number of issues and impact of APOE4 remains unclear. For instance, there is inconsistencies regarding in what direction (decreases versus increase) activity alteration are seen, and due to the lack of more longitudinal follow up it is still obscure how the observed changes correspond to subsequent cognitive impairment (and ultimately AD development). Using longitudinal follow up data from Norwegian population this study among things seeks to assess if there would be significant statistical differences among carriers of APOE e4 and non-carriers. The interactive effect of gender as well as age would also be critical assess on task of episodic memory performance.

Hypotheses

Based on previous studies it was hypothesised that:

1. significant differences would exist in the score from the first as well as the second test in relation to gender as well as apoe4 status,
2. age would significantly impact on the recall of participants in both the first and the subsequent test.

CHAPTER THREE

METHODOLOGY

The data presented in the current study represent the first two time points of an ongoing longitudinal study examining cognitive changes in genetically at-risk individuals at the University of Oslo.

Participants

A total of 110 of 139 people who participated in the first phase of the study were used in the final analysis. They were recruited through advertisements in local newspapers. All participants were interviewed and probed for previous or present neurological or psychiatric diseases known to affect the central nervous system and for history of substance abuse. Any person with a history of treatment for any of the above was excluded from further participation. All participants gave their informed consent to their participation, including blood sample, DNA extraction and genotyping, and storage of remaining blood for up to 10 years in a "biobank" according to Norwegian regulations. The project was approved by the Regional Committee for Research Ethics of Southern Norway, and the biobank was approved by the Department of Health. The participants were given the California Verbal Learning Test II (CVLT–II) as a measure of memory function (Delis, Kramer, Kaplan, & Ober, 2000).

There were no sex, IQ, or memory score differences between genotype groups. *T* scores on CVLT–II verified that all within-group mean *T* scores were 50 or above with *SD*s around 10, which is the definition of a normal sample. Notably, *T* scores on CVLT–II were clearly higher than 50, consistent with the groups' high IQ scores. Thus, the measures most pertinent for diagnosing dementia or preclinical dementia indicated a normal sample. The participants also performed a wider selection of neuropsychological tests as part of another study, and the results will be reported elsewhere. The full neuropsychological protocols were examined by a clinical neuropsychologist experienced with assessments of dementia, and 1 participant was excluded from the study. Thus, not only was the sample non demented, it is highly unlikely that many participants were in early phase dementia. The group performed additional neuropsychological tests of attention and speed. Informed consent was obtained.

Procedure

The California Verbal Learning Test (CVLT) was included to obtain measures of verbal learning, recall and recognition, as well as learning strategies, error types, and serial position effects. In the learning task, the participants were presented to a list of 16 words (list A), where each word belonged to one of four categories. The list was presented and recalled five times before a second list (list B) was presented. The participants were immediately after the recall of list B asked to recall the words from list A, both in a free and cued recall condition. After an interval of 20 minutes, the participants were again asked to recall the words from list A in a free and cued recall and recognition condition.

DNA Extraction and Genotyping

Determination of APOE alleles was performed for all participants using high-molecular weight DNA that was extracted from peripheral blood leukocytes and amplified using the PCR method. Specific genotypes were identified by detection of fragment sizes of digested DNA using electrophoresis. This was performed by real-time PCR with allele-specific fluorescence energy transfer probes and melting curve analyses on the Light Cycler system (Roche Diagnostics, Mannheim, Germany). DNA was extracted from 300 μl whole blood using MagNA Pure LC DNA Isolation Kit–Large Volume on the MagNA Pure LC (Roche), eluted and diluted to 1 ml, of which 5 μl was applied in each assay. Typing of the APOE-ε2, -ε3, and -ε4 genotypes was performed using the Light Cycler APOE Mutation Detection Kit (Roche). The assay was performed as specified by the supplier, except for scaling down the total assay volume from 20 to 10 μl.

CHAPTER FOUR

RESULTS

Demographic information for the 110 participants who turn up for the second phase of the study is grouped by the presence or absence of the APOE ε4 allele as well as with regards to gender and presented in Table 1 below.

Table 1: Demographic data based age, education, MMSE, IQ and APOE e4 genotype

		AGE		EDUC		MMSE		IQ	
	N	M	S.D	M	S.D	M	S.D	M	S.D
APOE _-ve	**67**	**67.76**	**7.3**	**13.10**	**2.8**	**28.81**	**.99**	**120.69**	**12.0**
APOE_ +ve	**43**	**68.23**	**7.4**	**13.70**	**2.8**	**28.86**	**.80**	**122.93**	**10.1**
TOTAL	**110**	**67.95**	**7.3**	**13.34**	**2.8**	**28.83**	**.92**	**121.50**	**11.3**

Table 2: Demographic data based on gender and apoe4

GENDER	Males	Females	Total
Apoe4 (+)	17	26	**43**
Apoe (-)	15	52	**67**
Total	**32**	**78**	**110**

There were no group differences in age, education, or gender the task before and after the interval period. MMSE scores also did not differ with regards to APOE genotype. Additionally, participants IQ as measured at baseline. Number of years for educational attainment ranges between 7 years to 18 years and that corresponds to between high school and graduate school. The average mean education for both participants with positive APOE e4 genotype did not significantly differ with those with negative APOE e4 genotype. There were more women than men enrolled in this study, but there was no difference in gender ratios between groups. Participants were predominantly Norwegian Caucasians.

Table 3: Means and Standard Deviations for the two time periods based on APOE e4 Genotype

SOURCE	CVLT Long delay				CVLT Short Delay			
	Time I		Time II		Time I		Time II	
(N)	M	S.D	M	S.D	M	S.D	M	S.D
Apoe4 (+) (43)	12.37	2.6	11.06	3.6	11.37	2.7	10.64	3.7
Apoe4 (-) (67)	13.37	2.7	11.96	3.7	12.40	3.1	11.65	3.1
Total (110)	**12.76**	**2.6**	**11.41**	**3.6**	**11.77**	**2.9**	**11.04**	**3.5**

The general linear model, performed with SPSSv.16, was used to perform a repeated measures analysis of variance to evaluate changes in functioning from the first to second test. This procedure allows for a multivariate evaluation of multiple independent and dependent variables. A dichotomous variable coded for the presence or absence of the ε4 allele (APOE ε4+/–). APOE status (ε4+ versus ε4–) and Gender (Females and Males) were independent variables in the analysis, and California Verbal Learning Test (CVLT) on the first and second tests were entered as repeated measures dependent variables.

Table 4: A table showing the results of within group differences over the 4 year period based on gender, age and apoe4 dichotomy on short delay recall

SOURCE	df	Mean Square	F	Sig.
CVLT	1	12.473	1.271	.262
CVLT * AGE	1	.190	.019	.890
CVLT * GENDER	1	16.383	1.669	.199
CVLT * APOE_dic	1	.668	.068	.795
CVLT * AGE * GENDER	1	.226	.023	.880
CVLT * AGE * APOE_dic	1	3.249	.331	.566
CVLT * GENDER * APOE_dic	1	1.099	.112	.739
CVLT * AGE * GENDER * APOE_dic	1	10.186	1.038	.311
Error(CVLT)	102	9.816		

It has been hypothesised that significant differences would exist in the score from the first as well as the second test in relation to age, gender as well as APOE ε4 status. This was

however not confirmed by the results presented in Table 4 above. There were no within group differences in the testing interval between Exam 1 and Exam 2, which was approximately 4 years The results from Table 4 above indicate that none of the independent variables considered resulted in any significant changes over the period under consideration. The hypothesis that significant cognitive decline would be recorded over the period on short delay is therefore not supported. There was also no significant interactive effect within the groups, that is, age did not interact with APOE ε4 gene to bring any significant changes neither did the interactive effect of gender with APOE ε4 gene.

Table 5: A table showing the results of within group differences over the 4 year period based on gender, age and apoe4 dichotomy on long delay recall

Source	df	Mean Square	F	Sig.
cvlt	1	21.888	2.063	.154
cvlt * age1	1	3.316	.313	.577
cvlt * Sex	1	12.215	1.151	.286
cvlt * APOE_dic	1	5.165	.487	.487
cvlt * age1 * Sex	1	.099	.009	.923
cvlt * age1 * APOE_dic	1	15.356	1.448	.232
cvlt * Sex * APOE_dic	1	.263	.025	.875
cvlt * age1 * Sex * APOE_dic	1	8.375	.790	.376
Error(cvlt)	102	10.608		

It has also been hypothesised that, the recall of long delay interval, significant differences would exist in the score from the first as well as the second test in relation to age, gender as well as apoe4 status. As was with the recall of short delayed items, this was not confirmed by the results presented in Table 5 above. There were no within group differences in the testing interval between Exam 1 and Exam 2, which was approximately 4 years The results from Table 4 above indicate that none of the independent variables considered resulted in any significant changes over the period under consideration. The hypothesis that significant cognitive decline would be recorded over the period on long delay is therefore not supported. There was also no significant interactive effect within the groups, that is, age did not interact with apoe4 gene to bring any significant changes neither did the interactive effect of gender with apoe4 gene.

The average mean scores between the groups were also computed by the repeated measure and the results presented in Table 6 below.

Table 6: A table showing the results of between group differences over the based on gender, age and apoe4 dichotomy on short delay recall

Source	df	Mean Square	F	Sig.
AGE	1	5.242	.540	.464
GENDER	1	35.940	3.699	.057
APOE_dic	1	88.067	9.063	.003*
AGE * GENDER	1	10.837	1.115	.293
AGE * APOE_dic	1	43.168	4.443	.038*
GENDER * APOE_dic	1	11.947	1.230	.270
AGE * GENDER * APOE_dic	1	19.376	1.994	.161
Error	102	9.717		

From the results in Table 6 above, it could be noted that significant differences on short delay recall were observed between groups of cognitive normal individuals with APOE e4 positive genotype and those with negative APOE e4 genotype. Thus [F (3, 102) = 9.06, p <.003]. That is, on average from the two tests, cognitively normal individuals with APOE e4 positive genotype performed poorly on the task of short recall than their counterparts with negative APOE e4 genotype. There was also significant interactive effect between age and APOE e4 on the recall of short delayed items [F (3, 102) = 4.44, p <.038.] and this was based on the group average means. Thus although age does not significant affect recall on short delay, older participants with a positive status on apolipoprotein e4 allele obtained lower scores indicating that APOE e4 gene interacts with age to produce cognitive deficits in normal cognitive individuals.

The average mean scores on long delay recall were also computed and the results presented in the table 7 below.

Table 7: A table showing the results of between group differences over the 4 year period based on gender, age and apoe4 dichotomy on long delay recall

Source	df	Mean Square	F	Sig.
age1	1	18.099	2.053	.155
Sex	1	29.333	3.328	.071
APOE_dic	1	44.280	5.023	.027
age1 * Sex	1	9.964	1.130	.290
age1 * APOE_dic	1	11.203	1.271	.262
Sex * APOE_dic	1	5.371	.609	.437
age1 * Sex * APOE_dic	1	3.876	.440	.509
Error	102	8.815		

From the results in Table 7 above, it could be noted that significant differences on long delay recall were observed between groups of cognitive normal individuals with apoe4 positive status and those with negative apoe4 status. Thus [F (3, 103) = 5.03, p <.027]. That is, on average from the two tests, cognitively normal individuals with apoe4 positive genotype performed poorly on the task of long delayed recall than their counterparts with negative status on the APOE ε4 genotype.

Additionally, at .05 level of significance, age could not account for CVLT test score, neither in combination with apoe4 status, significant differences could be observed among participants on long delay. Thus the results from Table 7 above failed to support the hypothesis on age as well as interactive effect between APOE genotype and age for CVLT on long delay recall.

SUMMARY OF RESULTS

For change over, that is, within subjects

- there were no significant changes over time
- no significant interactive effects in changes (age, gender and apolipoprotein e4 genotype)

None of the differences were observed on both short delay as well as long delay recall.

For differences between groups averaged score (average time 1 and time 2 measurements)

- there was significant mean differences based on apoe4 status (participants with positive APOE ε4 allele have lower average mean scores than participants with negative apoe4 allele (both on short and long delay recall).
- there was also an interactive effects between APOE ε4 genotype and age (only on short delay recall) with the difference between the positive and negative larger for adults age group.
- However no significant interactive effect was observed on the long delay recall. The results of the various test scores were presented in the tables below.

CHAPTER FIVE

DISCUSSION

The current study examined the effects of age, gender and APOE genotype on the rate of change on measures of delayed recall (short and long delay). A total of 110 of 139 people who participated in the first phase of the study were used in the final analysis from Norwegian population with the aim among things to assess if there would be significant statistical differences among carriers of APOE e4 and non-carriers. The interactive effect of gender as well as age was also critically assessed on task of episodic memory performance.

Based on previous studies, it was hypothesized that significant decline in cognitive abilities as measured by performances on the California Verbal Learning Test (CVLT) would be observed from the time 1 to time 2 which was approximately four year differences in measurement. It was believed that apolipoprotein genotype would significantly impact on cognitive decline over the four year period.

Further, it was hypothesized that age would significantly impact cognitive decline, with older adults significantly declining in cognitive ability over the study period. Gender was also hypothesized to impact cognitive decline based on previous studies done within this areas, notably, Herlitz, Nilsson, & Bäckman, (1997) and Kramer, Delis, Kaplan, O'Donnell, & Prifitera, (1997).

Finally, it was hypothesized that significant interactive effect would be observed between apoe4 status, age and gender on cognitive abilities as measured by the California Verbal Learning Test.

The summary of the results indicates that for a change over, that is, within subjects there were no significant changes over the period under consideration. No significant interactive effects in changes (age, gender and apolipoprotein e4 genotype) were observed on both short delay as well as long delay recall.

For differences between groups averaged score (average time 1 and time 2 measurements), there was significant mean differences based on apoe4 status (participants with positive apoe4 allele have lower average mean scores than participants with negative apoe4 allele (both on short and long delay recall). There was also an interactive effect between apoe4 genotype and age (only on short delay recall) with the difference between the positive and negative larger for adults' age group with positive APOE e4 genotype. However no significant interactive effect was observed on the long delay recall.

The current study however confirms some of the previous studies (e.g. Caseli et al 1999; Bondi et al 1999; Nilson et al 2006 etc). Casselli and colleagues (1999) contended that age related memories decline occurs earlier in cognitively healthy APOE e4 monozygotes than in APOE e4 heterozygotes and non- carriers. In their study that was based on cross-sectional evaluations of non-demented individuals, test of immediate and delayed recall revealed significant negative correlation with age in the APOE e4 monozygotes group relative to other non-carriers groups. In the present study, older participants with positive APOE 4 status showed decline (although not statistically significant) over time and in the same age group significant lower scores were observed on test of delayed recall as compared to younger adults without the APOE e4 allele.

The current findings also confirms previous study by Bondi and colleagues (1999), whose participants at baseline did not differ on age, gender, education or global cognitive status but had found significant lower scores for non-demented older adults with APOE e4 allele on delayed recall. They however failed to find any significant group differences on executive functions as well as attention. Bondi and colleagues however cautioned that episodic memory decrements among individuals with an APOE e4 allele do not necessarily reflect the direct influence of APOE e4 genotype on cognition and that what appears to be the case in the group differences is the inclusion of significantly more individuals with incipient dementia with the e4 group.

In the current study, the effect of APOE e4 allele alone seem to be just at minimal as indicated by the eta value and the effect size obtained from the statistical analysis. If this statistical value is anything to go by then the caution of Bondi et al (1999) need to be taken into consideration before making any generalised conclusions on the effect of APOE e4 genotype on cognition. Further, in the present study delay recall ability declined in a group of cognitively normal individuals who have the APOE ε4 allele, but this decline was observed only in individuals who were age 60 years or older. There was no significant change in new learning over the 2-year interval in the younger ε4+ group or individuals who do not have the ε4 allele. Thus, these findings suggest that the ε4 allele affects new learning in otherwise cognitively normal individuals, but that this effect may not be evident in younger individuals.

The importance of using longitudinal studies in this field cannot be ignored as it provides researchers with baseline upon which a measure of cognitive and other memory decrements over time can be assessed. As with the current study, longitudinal studies provide the evidence for the cognitive decline as a result of APOE e4. Among some of these studies

which the current findings find support include a study by Wilson et al (2002) in which a series of random effect models found that e4 was associated with impaired baseline function in episodic memory. The effect on annual decline in episodic memory was significantly stronger than its effect on decline in other cognitive domains and thus concluded that APOE e4 allele influences risk of AD by a relatively selective effect on episodic memory.

Substantial literature suggests that the ability to acquire and retrieve new information typically declines with age, whereas recall of remote information is generally stable, however, the bases of the age-related changes according to Craik (1991) are ill defined. Less efficient central processing (Baddeley, 1986), smaller storage capacity or both may account for age-related memory deterioration. Moreover, the extent of age-related changes in acquisition and retrieval appears to vary depending on a variety of modulating factors as for example in the person's APOE e4 genotype. Although the exact extent and nature of changes in memory associated with normal aging remain to be denned, the demand on clinicians to distinguish between normal age-related memory changes and abnormal disease-induced memory changes persists.

The current study found age to significantly interact with APOE e4 genotype to produce significant cognitive decline. This study thus replicates previous studies (e.g. Nilson et al., 2006). For instance Nilson and colleagues (2006) found a more pronounced epilson 4 related deficits for participants 70 years or older and in particular task assessing episodic recall. In the study Nilson and colleagues found that the presence of the ε4 allele does not have a general effect on memory performance but rather, the magnitude of ε4-related deficits are primarily observed in tests of episodic memory, with little effect in tests of semantic memory, and no effect in tests of primary memory and priming. Additionally, as in the case of the current study, they found that the episodic memory impairments were more pronounced in tests of recall than in tests of recognition memory. On the basis of the data obtained Nilson and colleagues (2006) suggest that analyses of the effect of specific genes on cognitive function should be accompanied by assessment of cognitive performance at a specific level.

It is very important to note that the current study, however, failed to confirm some of the previous researches conducted in this topic. Notably among is the conducted by Small and colleagues (2000) who examined the relationship between APOE genotype and cognitive functioning in normal aging, and to determine whether this relationship was moderated by

age or the presence of a normal of disease conditions including cardiovascular diseases and diabetes. Although mean level results indicate that groups with or without the APOE epilson 4 allele performed similarly on all the domains of cognitive functions, as in the case of the current study, Nilson et al (2000) however, found significant age group differences for episodic memory. Additionally, significant gender difference was present for episodic memory and stroop task. Finally, their study also demonstrated that participants' age did not exert any impact on the relationship between APOE epilson and cognitive functioning. These findings are however at variance with the current findings which did not find any significant impact of age nor gender alone on cognitive functioning but rather found significant interactive effect between age and APOE epilson on episodic recall.

Similarly, Salo et al (2001) also failed to confirm the hypothesis that poor cognitive performance is associated with the apoe4 allele and good performance with the APOE-e2 allele in the oldest old when they analysed the relationship of the apolipoprotein E e4 and e2 alleles to learning and memory performances in the non demented oldest old. In conclusion, Salo and colleagues (2001) contended that their results are consistent with an evolving idea questioning the role of the APOE genotype in influencing learning and memory in the oldest old. Just as the association between the APOE -e4 allele and Alzheimer Diseases seems to decrease with increasing age, so too does the association between the APOE - e4 allele and poor performance seem to decrease or even disappear on tests assessing learning and delayed memory (Salo et al, 2001). This may indicate that individuals who reach a very old age without becoming demented may represent a selected group of survivors. APOE affects the risk of AD, but does not necessarily alter normal brain function. Those very old, non-demented APOE -e4 individuals could be an important resource for identifying environmental and genetic factors that decreases the risk of dementia, concluded Salo and colleagues.

The current findings failed to support the assumptions that age alone would impact cognitive decline. There was however, a support for the findings which indicates that age interacts with APOE e4 genotype to impact cognitive decline. Additionally, the current findings failed to confirm Mayeux eat al 2001; Dik et al. 2000 etc. Thus on the level of intergroup differences, age becomes significant factor in cognitive decline only if it is related to APOE status of the participants. In line with Mayeux et al (2001) who also found that memory performance declined over time in healthy elderly individuals without AD or QD, but other cognitive skills

remained stable. Increased age was associated with lower scores in all cognitive domains while increased education was associated with higher scores. APOE-e4 was not associated with poor performance in any cognitive domain at any specific time interval. However, there was a statistically significant relationship between APOE-e4 and change in memory performance over time in the healthy elderly group, the only part which is confirmed by the current study.

Dik et al (2000) also found APOE-epsilon4 to be associated with memory decline in subjects with cognitive impairment, but not in normally functioning subjects, and suggested that the risk of APOE-epsilon4 on memory decline does not decrease at higher ages. The current study thus contradicts this finding by Dik et al (2000). In the present study memory decline was observed only in individuals who were age 60 years or older and carries and the APOE e4 genome.

The present study also aimed at finding out the role of gender in cognitive decline on normal aging and its relationship with APOE e4 genotype in this direction. Results, however, indicate that there is no significant statistical relationship between gender and cognitive decline as well an insignificant interactive effect between gender and APOE e4 genotype. The current study thus failed to support the hypothesis that significant gender differences would be observed and thus failed to support most of the previous studies. Initial studies (Maccoby and Jacklin, 1974) may not have found gender differences in memory, later studies (e.g. Herlitz, Nilson, & Bäckman, 1997; Kramer et al, 1997), however, tend to find gender differences favouring women on episodic memory.

For instance the results from Herlitz et al (1999) suggest that women perform at a higher level than men on verbal episodic memory tasks and on some episodic memory tasks with a visuospatial component. Episodic memory was assessed in tasks that, to a greater or lesser extent, were verbal or visuospatial in nature. Results showed that women excelled in verbal production tasks and that men performed at a superior level on a mental rotation task. In addition, women tended to perform at a higher level than men on most episodic memory tasks. However, the present findings failed to replicate this. Herlitz and colleagues concluded that although women's higher verbal production abilities contribute to their higher performance on episodic memory tasks, it cannot fully explain the female advantage seen in the majority of such tasks. A possible reason for this could be that educational level, which

the current study failed to looked, may have played a role. It could be that education played a role as a buffer for the men such that they performed similarly as the women on the episodic task. Due to the limited amount of research focusing on sex differences in episodic memory, very few explanations of the female advantage have been proposed. Because the bulk of relevant research has involved verbal material, it has been suggested that the advantage women have over men on episodic memory tasks may be specific to verbal material. Taking educational level into consideration may have provided the clue to the current findings.

Whilst previous studies found significant interactive effect of gender and apoe-e4 allele on episodic memory (e.g.Swan et al, 2005; Lehman et al, 2006, etc) the current study failed to replicate these findings. For instance, Swan and colleagues found significant gender and APOE ε4 interaction for change in performance on short delay cued recall where the findings showed that men with ε*4* experienced the greatest decline in short delay cued recall of all 4 subgroups.

The mechanisms for these selective effects are largely unknown but may be related to several sources. For instance, Parasuraman et al. (2002) reported ε4-related deficits on tests of attention and working memory.
Given the importance of these component abilities for successful episodic memory performance this may help to explain why this overall ability is deficient among ε4 carriers. The reason for this might simply be a theoretical ambiguity in how to classify the fluency test. At the time when the Betula Study started, fluency tests were regarded as tests of semantic memory in that they measured the generation of words from the internal lexicon (e.g., Kausler, 1982, 1991; Salthouse, 1991). In line with this, we also conceived of fluency tests as assessing semantic memory (e.g., Ba¨ckman & Nilsson, 1996; L.-G. Nilsson et al., 1997). However, in recent years, fluency tasks have also been seen as tasks assessing executive functioning (e.g., de Frias et al., 2005; Salthouse, Atkinson, & Berish, 2003). Viewed this way, the structure of the data pattern obtained here seems much clearer. The ε4 allele does affect episodic memory.

A possible neuronal explanation for the selective episodic memory deficit concerns the neural seat of APOE-ε4 related changes. Studies particular (Cohen, Small, Lalonde, Friz, & Sunderland, 2001; Moffat, Szekly, Zonderman, Kabani, & Resnik, 2000) have reported that ε4 carriers exhibit smaller hippocampal volumes relative to non-ε4 carriers. Given the

importance of this brain region for successful episodic memory functioning, this may help to explain the selective memory deficits. A two phase study by Lind et al (2006) found a reduced hippocampal volume in ε4 carriers and a reduced functional brain activity in the left inferior parietal cortex, and bilaterally in the anterior cingulated region, in ε4 carriers. In a latter study, they also observed a dose-related response in the parietal area such that diminution was most pronounced in homozygous compared with heterozygous carriers of the ε4 allele (Lind et al., 2006). Previously, Smith (2002) had noted in a review of the literature on APOE and aging that (a) APOE-deficient mice have defective mossy fiber sprouting that is rescued by ε3, but less so by ε4, (b) the alleles of APOE vary in their neuroprotective capacity with ε4 showing the least protective activity, and (c) elderly ε4 carriers have altered regional cerebral blood flow and hypometabolism in the entorhinal cortex that could predict future cortical/hippocampal hypometabolisms as well as cognitive decline. Wilson et al. (2002) also noted that several studies have demonstrated that the ε4 allele is less effective in neuronal repair than the other APOE alleles.

A final reason for the greater declines among ε4 carriers may be related to the presence of preclinical cases of AD. As noted by Wilson et al. (2002), there is an association between ε4 and level of AD pathology, in particular B-amyloid accumulation. This is obviously a major concern with respect to the data by Wilson et al.(2002) because no attempt was made to exclude participants who were diagnosed with AD after the cognitive data had been collected.

By using a longitudinal analysis, memory change as a function of age could be assessed; this may be a more sensitive measure of subtle memory decline. Although the current study suggests that the onset of memory decline in ε4+ carriers may be variable, there was relatively narrow range of individuals over 60, which may have limited current ability to detect the relationship between age alone as an independent variable and memory decline. Additional time points will help address whether there is a linear or accelerated decline in memory as these individuals age.

Strength and limitations

An advantage of a longitudinal design is that each participant serves as their own control which helps to increase observational power by offsetting cohort and other effects when assessing change in memory functioning over time.

Despite this advantage, the group size, especially the ≥60 ε4+ group, is relatively small. The groups compared in this study were similar in educational attainment and on the whole had above average verbal intellectual functioning compared to the general population. Higher education and verbal intellect has been associated with greater preservation of cognitive functioning during aging, and that may have affected our ability to observe memory dysfunction in the younger individuals with the ε4 allele. The majority of participants were Caucasian which may potentially limit generalization to other groups.

The effect of gender was evaluated, since there were more females than males in each group and accounting for gender in our analysis did not alter the findings. The interval between exams varied from approximately 3 to 4 years; however, there were no differences in interval length between the groups. Whether the influence of the ε4 allele on memory decline in present study is part of the neuropathological changes associated with AD will be based on conversion rates and further longitudinal evaluation of these individuals.

Several limitations should be noted. First, findings in this selected group may not generalize to other groups. Participants were predominantly Caucasian whites, and there could be evidence that APOE effects differ in other ethnic/racial groups. It is possible that within-group similarities in lifestyle may have helped to highlight the behavioural effects of genetic differences by reducing the confounding effects of other environmental variables associated with cognitive decline and AD. Additionally, the sample may be highly educated, and therefore, results may not be generalizable to the population as a whole. Also, no attempt was made to control for effects of educational background.

Finally, a longer period of longitudinal design would have advantages for investigating the natural history of the AD prodrome as a function of APOE genotype.

The finding that the ε4 allele has a detrimental effect on episodic memory only is encouraging for the memory systems view proposed by Tulving (1972, 1983, 1987). This dissociation adds, in a fundamental way, to the converging evidence presented by Nyberg and Tulving (1996) in terms of functional, developmental, pharmacological, and brain damage dissociations in human memory.

Thus, the present finding of a differential effect of presence or absence of the ε4 allele on episodic memory supports current memory theory in a new and intriguing way. Perhaps even more important for memory theory is the finding of dissociation between the two subsystems

of episodic memory. Although the distinction between recall and recognition is not new in memory research, the model recently proposed by Nyberg et al. (2003) presents a new angle to this issue. The more pronounced deficit in recall than in recognition indicates problems with executive processes, such as attention or working memory, as such processes are more heavily taxed by tests of recall (e.g., Craik, 1983 cited in Nyberg et al, 2003). In support of such an interpretation, previous studies have found observed ε4-attentional deficits (Parasuraman et al., 2002).

Conceivably, more complete understanding of the relationship between genes and memory requires consideration of a variety of factors. Several genes in interaction might account for a considerable portion of memory performance. After several candidate genes are known, this may be a fruitful approach. It is obvious that the role of genetics on memory function is a new challenging area of research, which requires focus of attention and efforts. Additionally, the role of culture and race in conjunction with genes on memory function should also be the focused of attention for researchers since most of these previous studies were mainly carried on Caucasian and particular most developed countries. If researchers can also begin to look at more traditional societies or multi-racial researches then the issue of generalization will certainly be overlooked.

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